

Clinical Policy: Denosumab (Prolia, Xgeva)

Reference Number: CP.PHAR.58

Effective Date: 03/11

Last Review Date: 08/17

[Coding Implications](#)
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for denosumab (Prolia® and Xgeva®).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that Prolia and Xgeva are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Osteoporosis (must meet all):

1. Request is for Prolia;
2. Diagnosis of osteoporosis evidenced by one of the following (a or b):
 - a. T-score \leq -2.5 by dual energy X-ray absorptiometry (DXA) at the femoral neck, spine, or total hip;
 - b. History of osteoporotic fracture confirmed by radiographic imaging;
3. If female, member is postmenopausal;
4. Age \geq 18 years or documentation of closed epiphyses;
5. Failure (decline in bone mineral density [BMD] of \geq 5% or continued fractures) of both of the following (a and b), each trialed for one year unless contraindicated or clinically significant adverse effects are experienced:
 - a. An oral bisphosphonate (e.g., alendronate, risedronate);
 - b. Zoledronic acid (Reclast) **requires prior authorization**;
6. If member has received zoledronic acid (Reclast), it has been at least one year since it was last administered;
7. At the time of request, member does not have any of the following contraindications:
 - a. If female, pregnancy;
 - b. Concomitant use of Xgeva;
8. Recent (within the last 90 days) lab result confirms that member does not have hypocalcemia (serum calcium or albumin-corrected calcium level must be within normal limit);
9. Dose does not exceed 60 mg every 6 months.

Approval duration: 12 months

B. Prostate or Breast Cancer Treatment – Induced Bone Loss (must meet all):

1. Request is for Prolia;
2. Diagnosis of one of the following (a or b):
 - a. Female with breast cancer receiving adjuvant aromatase inhibitor therapy;
 - b. Male with nonmetastatic prostate cancer receiving androgen deprivation therapy;

3. Age \geq 18 years or documentation of closed epiphyses;
4. Prior to therapy, meets one of the following (a, b, or c):
 - a. T-score \leq -2.5 (DXA) at the femoral neck, spine, or total hip;
 - b. History of osteoporotic fracture confirmed by radiographic imaging;
 - c. T-score $<$ -1.0 (DXA) at the femoral neck or spine, and one additional risk factor:
 - i. 10-year probability of hip fracture \geq 3% per the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX);
 - ii. 10-year probability of a major osteoporosis-related fracture \geq 20% per the WHO FRAX;
 - iii. Age $>$ 65 years;
 - iv. Glucocorticoid therapy at daily dosage equivalent to \geq 7.5 mg of prednisone for at least 3 months;
 - v. Parental history of hip fracture;
 - vi. Low body mass index (BMI $<$ 20 kg/m²);
 - vii. Current cigarette smoking;
 - viii. Excessive alcohol consumption (\geq 3 drinks/day);
 - ix. Rheumatoid arthritis;
5. At the time of request, member does not have any of the following contraindications:
 - a. If female, pregnancy;
 - b. Concomitant use of Xgeva;
6. Recent (within the last 90 days) lab result confirms that member does not have hypocalcemia (serum calcium or albumin-corrected calcium level must be within normal limit);
7. Dose does not exceed 60 mg every 6 months.

Approval duration: 12 months

C. Bone Metastases, Giant Cell Tumor of Bone, Hypercalcemia of Malignancy (must meet all):

1. Request is for Xgeva for one of the following purposes (a, b, or c):
 - a. Prevention of skeletal-related events in the presence of bone metastases from solid tumors (does not include multiple myeloma), and both (i and ii):
 - i. Age \geq 18 years or documentation of closed epiphyses;
 - ii. Dose does not exceed 120 mg every 4 weeks;
 - b. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and both (i and ii):
 - i. Meets one of the following age requirements (a or b):
 - a) Age \geq 18 years;
 - b) Age 13 through 17 years with skeletal maturity (defined by at least 1 mature long bone, e.g., closed epiphyseal growth plate of the humerus) and a history of body weight \geq 45 kg;
 - ii. Dose does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy;
 - c. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy, and all of the following (i, ii, and iii);

- i. Age \geq 18 years or documentation of closed epiphyses;
 - ii. Albumin-corrected calcium $>$ 12.5 mg/dL despite treatment with intravenous bisphosphonate therapy in the 30 days prior to initiation of Xgeva therapy;
 - iii. Dose does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy;
2. At the time of request, member is not using Prolia concomitantly;
 3. Recent (within the last 90 days) lab result confirms that member does not have hypocalcemia (serum calcium or albumin-corrected calcium level must be within normal limit).

Approval duration: 6 months

D. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. All Indications Specified in Section I (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy (if hypercalcemia of malignancy, has not achieved complete response as indicated by corrected serum calcium $<$ 10.8 mg/dL);
3. If request is for a dose increase, new dose does not exceed:
 - a. Prolia: 60 mg every 6 months;
 - b. Xgeva: 120 mg every 4 weeks.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy.

Background

Description/Mechanism of Action:

Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Prolia binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Xgeva binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of

osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

FDA Approved Indications:

Prolia (denosumab) is a RANKL inhibitor/subcutaneous injectable solution indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture*. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures;
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture*, or patients who have failed or are intolerant to other available osteoporosis therapy;
- Treatment to increase bone mass in men at high risk for fracture* receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures;
- Treatment to increase bone mass in women at high risk for fracture* receiving adjuvant aromatase inhibitor therapy for breast cancer.

**High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.*

Xgeva (denosumab) is a RANK ligand (RANKL) inhibitor/subcutaneous injection indicated for:

- Prevention of skeletal-related events in patients with bone metastases from solid tumors. Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Appendices

Appendix A: Abbreviation Key

BMD: bone mineral density	RANK: receptor activator of nuclear factor kappa-B
BMI: body mass index	RANKL: RANK ligand
DXA: dual energy X-ray absorptiometry	WHO: World Health Organization
FDA: Food and Drug Administration	
FRAX: Fracture Risk Assessment Tool	

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

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date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0897	Injection, denosumab, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Reviewed with no clinical changes.	02/12	03/12
Reviewed with no clinical changes.	03/13	04/13
Added FDA indication for giant cell tumors	03/14	03/14
Added FDA indication for hypercalcemia of malignancy. Updated background and safety information.	02/15	03/15
Changed approval periods to initial 3 months and continuation 6 months Converted algorithms into bullet points and adopted new template Removed Zometa and pamidronate trial as prerequisite for Xgeva In Reauthorization algorithm, removed question on ONJ and for giant cell tumor, removed question about 3 months of treatment and MRI/CT indication to continue treatment and added point that there is no indication of disease progression Removed Table 1 safety concerns	08/15	10/15
Prolia split from CP.PHAR.20.Osteoporosis Injection Therapy, converted to new template and combined with Xgeva into denosumab policy. Criteria updated as follows: added max dosing, definition of bisphosphonate trial failure and, if contraindication/intolerance, that it be to one of the two oral drugs listed and to Reclast. Calcium/vitamin D requirement language edited to be less specific. Osteoporosis criteria: for men with osteoporosis, criteria added to require testosterone for hypogonadal osteoporosis. Added “at femoral neck or spine” to T score. Added FRAX criteria for fracture risk. Removed requirement that patient must be over 50 in cases where the osteoporosis diagnosis relies on history of an osteoporotic fracture. Cancer treatment induced bone loss criteria: risk of fracture criteria in these populations is informed by FRAX calculations/recommendations. Criteria changes to Xgeva: For members under 18 with giant cell tumor of the bone, added definition of skeletal maturity per PI. Added max dosing.	02/16	03/16
Edited I.A.4. to acknowledge option “c” – “T-score <-1.0...” by stating “one of the following” rather than “a or b”. Under Section B, “Prostate or Breast Cancer Treatment – Induced Bone Loss”, removed requirement that member fail prior bisphosphonate therapy, particularly Reclast therapy, as Reclast does not have an analogous FDA approved indication.	06/16	08/16

Reviews, Revisions, and Approvals	Date	Approval Date
Under Section B, “Prostate or Breast Cancer Treatment – Induced Bone Loss”, amended criteria 4 to allow coverage of osteopenic members (T score < -1.0) with one additional risk factor for fracture.	08/16	08/16
<p>All indications: Modified age requirement to apply to pediatric members with open epiphyses. Removed requirement for administration of calcium/vitamin D. Removed hypersensitivity contraindication. Split hypocalcemia contraindication into its own criterion and specified time frame for which lab result is acceptable.</p> <p>Osteoporosis: removed criteria related to males with primary osteoporosis or hypogondal osteoporosis, and removed coverage of osteopenic members [T score < -1.0]. Osteoporosis, prostate or breast cancer treatment-induced bone loss: Added “at total hip” to T score; added that osteoporotic fracture should be confirmed by radiographic imaging. Bone metastases, giant cell tumor of bone, hypercalcemia of malignancy: Modified initial/re-auth approval durations from 3/6 months to 6/12 months.</p> <p>Re-auth: Combined Prolia and Xgeva criteria sets; added requirement for documentation of positive response and max dosing; removed reasons to discontinue.</p>	06/17	08/17

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

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This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for

members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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